REMARKS

Amendments to the Claims

The present amendment is submitted in an earnest effort to advance the case to issue without delay.

Independent claim 1, 2, 15 and 17 have been amended without prejudice to make the meets and bounds of the invention more clear and definite and to recite a preferred embodiment of applicant's invention that is more clearly differentiated from the prior art. These amendments are discussed in detail below in the section responding to the §112 rejections.

Support for amended claim 1 is found in the specification as filed on: page 15, lines 6-8; page 10, lines 6-10; page 10, line 27 – page 11, line 2; original claim 24, page 11 lines 8-28; page 12, line 7; page 12, lines 9-28; page 14, lines 9-18; and page 12, lines 21-28.

Amended claim 17 is a restatement of the method described on page 38, lines 18-27 as positive process steps.

Claim 27 was amended to increase the lower value of N recited in order to make the claim consistent with the amended claim 1.

Claim 24 has been canceled as its subject matter has been incorporated in amended claim1.

Claims 3, 7-14 16, 18-23 and 28-48 are withdrawn following an election filed under 35 USC§ 121 dated September 28, 2006 in response to a restriction requirement dated September 5, 2006.

Claims Rejection – 35 USC §112

Claims 15 and 17 were rejected under 35 USC §112 ,first paragraph as failing to comply with the enablement requirement.

Claim 15 has been amended to recite that the Multi-Pathway High Throughput Assay to be used in connection with the method of claim 1 predicts the "amelioration" of acne. Since the Examiner stated on page 4 of the Office Action that claims 15 and 17 were enabled for "ameliorating" acne, applicant assumes that amended claims 15 and 17 are fully enabled.

In view of the amendments and above remarks, applicant respectfully requests that the 112 first paragraph rejection of claims 15 and 17 be reconsidered and withdrawn.

Claims 1-2, 4-6, 15, 17 and 24-27 were rejected under 35 USC §112, second paragraph as being indefinite. Applicant submits for the reasons set forth below that amended claims 1 and 17 fully and definitely point out the metes and bounds of the invention under examination and are supported by the specification as filed.

Claim 1

With regard to claim1, the following changes have been made to the description of the process. Their enablement is discussed below:

Step i has been amended to clarify that the library to be selected is composed of ingredients that are to be tested as potentially biologically active

agents (Page 15, lines 6-8). These components of the library need not have known biologically activity although they can.

Step ii. has been amended to clarify that it is the assay that targets a biological end effect.

Original Step iii is actually composed of two steps: carrying out a dose response study on selected S(1) components to determine a specific concentration to be used in further testing in combination with the library and then testing the new combinations to identify further active combinations. For clarity, these two steps has been separated into the two steps recited in amended Steps iii) and amended Step iv)

Amended Step iii recites carrying out a dose response study on S(1) to identify a concentrations to be used in step iii) that has less than maximal effect on the assay (defined as $\lambda\ C_{Max,1}$, where λ is a scaling factor in the range from about 0.01 to 0.5, and $C_{Max,1}$ is the maximum activity measurable in the assay) (pages 10-11 paragraphs b) and c))

Applicant submits that a person skilled in the art to which the invention pertains (e.g., a trained molecular biologist or biochemist with 3-5 years of experience in high throughput in-vitro testing) reading the specification would readily appreciate that the Multi-Pathway High Throughput Assays meant to be used in the method of claim 1 would have to have a known practical working range (page 9, lines 9-14). That is, the skilled artisan would recognize that the assay would first need to be validated in terms of its precision and accuracy in response to test ingredients as well as its lower and upper limits of detection, e.g., through the use of positive and negative controls .

Applicant further submits that the skilled artisan would readily appreciate what step iii involves. Namely, that a dose response curve of the individual S(1)

active that displays significant activity is measured alone in the assay and then the concentration of this active is fixed so that its activity in the assay is some fraction (e.g., <0.5) of the maximum activity. The skilled artisan would recognize that the fraction λ that is used will depend on the detailed shape of the dose response curve (as stated on page 10, lines 18-20). The idea, enunciated in the specification, which applicant submits is well within the grasp of the skilled artisan, is to reduce the concentration of each S(1) ingredient so that when each S(1) ingredient is combined with each member of the library during binary testing, the combined response will likely be on a sensitive portion of the dose response curve.

Amended Step iv (original step iii) has been amended to eliminate the "scaling back" verbiage and simply state that the concentration of S(1) used in the binary testing is that value determined from the dilution study carried out in amended Step iii.

Original Step iv is actually composed of two steps: carrying out a dose response study on selected S(2) mixtures to determine a specific concentrations to be used in further testing in combination with the library and then a testing round to identify new combinations that are active . For clarity, these two steps have been separated into the two steps recited in amended Steps v and amended Step vi

Amended Step v essentially recites carrying out a dose response study on one or more of the S(2) binary mixtures identified in Step (iv), wherein the concentration of each component of the S(2) mixture is independently varied and the activity of the mixture is measured in the assay being used. These measurements provide the concentrations for each of the components of the one or more S(2) mixtures that gives each S(2) mixture to be subsequently tested less than maximal activity in the assay, i.e., an activity of $\lambda\ C_{Max,1}$. (as discussed on page 11, paragraph e).

Applicant submits that the skilled artisan reading the specification will quickly grasp that the idea behind this part of the process is to reduce the activity of the binary mixture so that the assay will be most responsive to any synergistic ternary mixture constructed. Furthermore, as the Examiner has noted, the skill of those in this art is high. Multi-component dose response studies are well known as are computer programs providing multi-variant analysis, which are available and commonplace in this art.

Amended Step v has two changes relative to original Step iv. Firstly, the "scaling back" verbiage has been eliminated and replaced by a simple statement that the concentration of each S(2) component used to construct the single ternary mixtures (with that S(2) component) in combination with each member of the library are those concentrations determined from amended Step iv. Secondly, the ternary testing step is now not optional.

Original Step v has been deleted and replaced by four additional steps: added Step vii – added Step xi.

Added Step vii essentially recites carrying out a dose response study on one or more of the S(3) ternary mixtures identified in Step (vi), wherein the concentration of each component of the S(3) mixture is independently varied and the activity of the mixture is measured in the assay being used. These measurements provide two outputs. Firstly, the concentrations for each of the components of the one or more S(3) mixtures that gives each S(3) mixture less than maximal activity in the assay, i.e., an activity of $\lambda\ C_{Max,1}$. (as discussed on page 11, paragraph e)) which will be used subsequently to construct S(4) combinations in step viii.

The second output of Step vii is the possible elimination of components of each S(3) mixture that no longer make a significant contribution to the activity of the ternary mixture. This is discussed on page 12, line 21 – 28.

Applicant submits that the skilled artisan would readily understand how to carry out this step because multi-component dose response studies are well known in this art and computer programs providing multi-variant analysis of the results are routinely used to generate multi-dimensional dose response equations and surfaces.

Applicant further submits that the skilled artisan having read applicants specification (e.g., page 12, lines 21-28) would readily be able to identify components of each ternary mixture that makes low or no contribution to the activity of the mixture. For example, skilled artisans in this art frequently carry out multi-variant analysis to generate equations that link activity of a mixture to its constituent components. Identifying components that make small contribution to overall activity of mixtures is commonplace and involves looking for relatively small coefficients in the correlation equations and matrices. This does not require any further experimentation beyond what is recited in the first part of step vii.

Applicant has purposely not placed a quantitative limit on the contribution made by an ingredient to be qualified as "marginal" because this depends on such things as the particular biological target, the cost and the availability of the material, etc. For example, an antibacterial agent contributing at best a 5% reduction in bacteria to the mixture might be considered marginal because the efficacy of antibacterial compositions is usually measured in powers of 10. However, if the biological effect under study is hair re-growth, then a 5% contribution might be judged as not marginal. Applicant submits that what the skilled artisan would understand from Step vii is to look for potential ingredients that might be removed from the S(3) mixture to reduce its complexity.

Added Step viii simply involves additional optional testing of one or more of the S(3) found in amended Step vi in combination with substantially each component of the library to seek additional synergistic combinations. Again, the concentration of the S(3) component is the value found in added Step vii corresponding to an activity $\lambda C_{Max,1}$. The proviso regarding elimination of components of S(3) based on the tests carried out in Step vii has already been discussed and its intent is clear from page 12 lines 21-28.

Added Steps ix and x are simply generalizations of added Steps vii and viii (for N= 3 and 4) discussed above and indicate that the multidimensional testing of discovered active combinations and further combinatorial testing with the remaining components of the library can be repeated indefinitely (N >5) as is set forth in the specification on page 12, lines 1-5.

Claim 15

Claim 15 has been amended using active language to make it clearer that it is the assay that predicts the amelioration of acne.

Claim 17

Claim 17 has been amended to recite the IL-1-Induced Hypercornification Assay in terms of a series of clearly delineated positive process steps. Applicant submits that the skilled artisan would readily appreciate the scope of the method of claim 17 coupled with a reading of Example 3 (pages 36-39) and the references contained therein.

In view of the amendments and above remarks, applicant respectfully requests that the 112 second paragraph rejection of claims 1-2, 4-6, 15 17 and 24-27 be reconsidered and withdrawn.

Claims Rejection 35 USC §102

Claims 1-2 and 27 were rejected under 35 USC §102(b) as being anticipated by Stockwell et al (US 2002/0019011). Applicant traverses this rejection.

Stockwell et al discloses 3 broad approaches for testing synergy among compounds. These are:

Method (i) Test all possible combinations in a library of compounds regardless of their activity when tested as a single component (disclosed in paragraph 0100 and illustrated in Example 2 starting at paragraph 0128);

Method (ii) Test all possible binary combinations of only those components that were active in initial testing. This is the conventional approach to systematic discovery of synergy and is disclosed by Stockwell in paragraphs 0017, 0103 and 0127. The most effective binary combinations of entities can be further evaluated in higher order combinations again with only the most effective components found from initial testing.

Method (iii) Test a limited number of random combinations within a large library of compounds again regardless of their activity when tested as a single component in the assay. This is illustrated in Example 1 para 0119 onwards. A modification of this random testing is provided in para 0105 for the unusual situation where an underlying mathematical relationship between the activities of the members of the library allows a genetic algorithm to be used to direct the random testing to the most effective combinations.

Applicant's method rests on two fundamental insights gained through theoretical analysis and experimentation. Firstly, that in the most effective synergistic mixtures existing in a library of compounds, one or more of the individual compounds will have significant activity when tested by themselves in the assay.

Secondly, that successive and repeated testing of a limited number of the active compounds of the library in combinations with substantially all the members of the library in binary, ternary and higher order mixtures will lead to the identification of synergistic mixtures displaying the greatest activity.

The differences between the methods disclosed by Stockwell et al and applicant's are discussed in detail in the accompanying Declaration from Dr. Ian R. Scott (hereafter "Scott"), the inventor and a authority in skin bioscience. Applicant respectfully draws the Examiners attention to this declaration and especially the pertinent example contained therein which illustrates the key differences.

Applicant's method differs from those disclosed by Stockwell et al in among others, two key respects:

Firstly, in contrast to Stockwell et al, applicant repeatedly tests a limited number of effective components and synergistic mixtures found in single-components, binary and higher order testing in combinations with substantially each component in the library. This process is counterintuitive based on the teaching of the prior art as it involves ignoring a potentially large number of effective components and binary, and ternary synergistic combinations while continuing to retest chemicals which showed no effect either alone in the first cycle or in binary combinations in the second cycle, etc.

The second key difference is the use of single and multi-component scaling protocols (dose response testing) between successive combinatorial testing cycles of identified synergistic mixtures with substantially each component of the library. As discussed in the specification and in Scott's Declaration these protocols are interspersed between test cycles and are not taught by the prior art. The protocols have three critical functions:

- The concentrations of the active agents are continuously reduced as cycles are completed so that the combination of actives to which the test compound will be added has less than maximal efficacy in the assay. This provides mixtures for which the assay is most likely to have maximum sensitivity

- The testing process is streamlined and the number of experiments reduced relative to other methods because only one concentration of an active ingredient (i.e., from step (ii)) or only one composition of an identified synergistic mixture is tested in further cycling with substantially each component of the library. This approach is in stark contrast to the construction of a "compound dilution matrix" as taught, for example, by Borisy et al (see discussion below).

- At each stage, when the Multiple Component Scaling Protocol for the combination of actives is performed it may be found that actives that were very effective in early cycles have become marginally effective, their role being made unnecessary by the combinations of the other actives. In that case such actives may be eliminated from further cycles of testing. It is thus possible that a cycle where, for example, a ternary combination of agents is combined with the library, that the output to the next cycling with the library will be another ternary mixture, or even conceivably a binary mixture, rather than a quaternary mixture (specification page 12, lines 21-28 see also Scott)

The distinctions between applicant's invention and the methods set forth in Stockwell et al and their implications can further be understood by considering in detail Example 1 of Stockwell et al, which although stated to be hypothetical, is nevertheless highly instructive. Using applicant's nomenclature, Example 1 of Stockwell et al starts by selecting a "library" consisting of 768 compounds. All the members of this library are tested individually at two concentrations in an assay that targets "binding to different cells or tissue". Setting aside whether such an assay qualifies as a "Multipathway" assay, Stockwell et al report in FIG 3A – 3D that none of the compounds show any activity at the concentrations tested.

Stockwell et al then tests 368 binary pairs of the 768 compounds of the library even though none displayed any activity in the initial round of single component testing.

Of the 386 binary pairs, Stockwell et al then find one (1) pair that displays synergistic activity (e.g., receptor binding).

What Stockwell et al does not discuss is that only a very small fraction of the possible binary pairs are actually sampled. To understand this, we have to recognize that the total number of possible binary pairs that can be constructed from a Library of W compounds (e.g. 768) is

$(W \times W-1)/2 = (768 \times 767)/2 = 294{,}528$ possible binary pairs

Thus, the fraction of all the binary pairs actually sampled is 386/294,528 = 0.0013 or 0.13%. That is, only about 1 in a thousand of the possible pairs were tested.

Applying applicant's method to the same facts scenario would lead to a vastly different outcome than disclosed by Stockwell et al. Using the same hypothetical library, applicant's method would also begin by testing the 768 compounds of the library over a wide range of dosages. If in fact no compounds displayed any significant activity, over the reasonable range of concentrations tested, then no binary mixtures would be tested, i.e., the library as constituted would be abandoned!

However, applicant firmly believes that the behavior discussed in the *hypothetical* Example 1 of Stockwell is *not representative of real synergism* found in the types of biological end effects targeted by applicant's invention and especially in large libraries of compounds. Namely, that in the most effective synergistic mixtures existing in a library of compounds, *one or more of the individual compounds will have significant activity when tested by themselves in the assay.*

A more realistic hypothetical example is discussed by Scott in Items 11 and 12 of the accompanying declaration. Given the assumed fact scenario given on page 8 of the declaration, applicant's method identified the most effective binary synergistic combinations in a library of 100 chemicals and demonstrated that there were no synergistic ternary combinations displaying greater effectiveness. Applicant's method required 985 experiments.

In contrast, Scott shows on page 11 of the declaration that method (i) disclosed by Stockwell et al (test all possible combinations) would also identify the most effective binary mixture and also confirm that no ternary mixture is more effective. However, the number of experiments required to reach this answer is around 160,000 to around 4,000,000 assays by the random testing method depending upon whether a "compound dilution matrix" of Borisy et al was employed (see below).

Scott also shows that method (ii) disclosed by Stockwell et al (test only combinations wherein the individual components have activity) will not identify any of the synergistic binary mixtures because one or more of the ultimately synergistic components are not active when tested alone.

The above example set forth by Scott illustrates the key advantage of applicant's method which makes it an advance in the field of synergy testing. Namely, the inventive method allows interrogation of a large library of potential actives to identify the most effective synergistic mixture while keeping the experimental load manageable.

Absent disclosure of i) identifying compounds and mixtures of a library that have significant activity and only testing these compounds or mixtures (or a portion of these) with substantially all the remaining components of the library at least up to ternary mixtures, and ii) utilizing applicant's single- and multi-component scaling protocols between successive combinatorial cycling steps, Stockwell et al could not anticipate applicant's claims.

Neither does the reference render the claims obvious. By teaching either the random testing of all the combinations of components in a library even when none of the components of the mixture has significant activity, or testing only combinations of components that are active by themselves, and failing to teach applicants scaling protocol between testing cycles, Stockwell et al teach away from applicants method.

In light of the above remarks, applicant's respectfully requests that the 102(b) rejection over Stockwell et al (US 2002/0019011) be reconsidered and withdrawn.

Claims 1-2 and 24-26 were rejected under 35USC 102(a) as being anticipated by Borisy (US 2002/0165261). Applicant traverses this rejection.

Borisy et al is directed to a method of treating a patient having cancer by administration of a benzimidazole and pentamidine. The Examiner asserted that Borisy et al discloses in the abstract a method for identifying a synergistic mixture. Applicant submits that the words "library" or "synergy" do not appear in the abstract which is entirely directed to a method of treating a patient with cancer.

Borisy et al is silent about any general methodology for interrogating libraries of ingredients for synergy remotely resembling applicant's methodology.

The Examiner, citing Examples 1-3 of Borisy et al (e.g., Table 1), asserts that Borisy et al anticipates adjusting concentrations and the use of lambda factors (λ). However, applicant submits that the testing protocol disclosed by Borisy et al in these examples is completely different from applicants scaling protocols as the following discussion demonstrates.

In Example 1, Borisy et al constructs a standard "compound dilution matrix" (page 15, paragraph 0145) between two ingredients (active drugs) being tested. With reference to Table 1, a 100 mixtures of "A" (albenzadole) and "B" (pentamidine isethionate) are tested for activity at 10 concentrations of A and 10 concentrations of B (a 10x10 matrix). Mixtures which display maximum activity are then identified.

The procedure described by Borisy et al is in stark contrast to applicant's scaling procedure. This can best be understood by considering binary mixtures tested in the second round (Step iv of amended claim 1). Here, the dose response of a single component found to have significant activity by itself (S(1)) is measured alone (generally 5-10 experiments) and a single concentration providing the correct minimal activity is used in combination with other remaining components of the library. The concentration of these remaining ingredients used in the binary mixture is their concentration initially tested. The implications

of these differences in the testing process can best be appreciated by considering the following simple example.

Suppose the library to be interrogated for synergism contains 100 compounds and 5 compounds are found to have significant activity. If we apply the Borisy et al "compound dilution matrix" approach, to *applicant's protocol,* the number of experiments required is 50 x 950 = 47,500.

In applicant's scaling approach the number of experiments required is 50 (5 x 10 for scaling) + 5 x 95 = 525. Thus, applicant's scaling approach leads to a factor of 90 less experiments required to find synergistic combinations in this relatively small library.

For larger libraries the differences in terms of absolute experimental load becomes dramatic (e.g., factors of 1000's).

Thus, Borisy et al in fact teaches away from applicants scaling procedure by requiring all components present in the binary mixture be tested at multiple concentrations.

Absent disclosure of: i) identifying compounds and mixtures of a library that have significant activity and only testing these compounds or mixtures (or a portion of these) with substantially all the remaining components of the library up to at least ternary mixtures, and ii) utilizing applicant's scaling protocols between combinatorial cycling, Borisy et al could not anticipate applicant's claims.

In light of the above remarks, applicant's respectfully requests that the 102(a) rejection over Borisy (US 2002/0165261) be reconsidered and withdrawn.

Claims Rejection 35 USC §103

Claims 4-6 were rejected under 35 USC 103(a) as being unpatentable over Stockwell et al (US 2002/0019011) as applied to claims 1-2 and 27 above in view of Granger (WO 02/02074). Applicant traverses this rejection.

In applicants' method all the components of the library are first tested and then combinations are only formed between a component which displays significant activity and each of the remaining components (with appropriate selection of concentration). Higher order combinations are constructed in an analogous fashion.

In contrast, as discussed above, Stockwell et al teaches the interrogation of a library of compounds for synergy either by testing all combinations (or a random part of all combinations) of members of the library including combinations in which all components have no measurable activity, or the testing of combinations of only active components. This approach either leads to unmanageably large numbers of experiments when large libraries are involved or has a high probability of missing the most effective synergistic mixtures.

Absent disclosure of: i) identifying compounds and mixtures of a library that have significant activity and only testing these compounds or mixtures (or a portion of these) with *substantially all the remaining components* of the library up to at least ternary combinations, and ii) applicant's scaling protocol used between combinatorial cycling, Stockwell et al does not present a *prima facie* case of obviousness.

Furthermore by teaching the testing of random combinations of members of the library including combinations in which all components have no measurable activity or alternatively teaching only the testing of combinations

where all the components must have activity on their own, Stockwell et al in fact teaches away from applicant's claimed invention.

Granger et al does not remedy the shortcomings of Stockwell et al as a prior art reference. Granger et al is directed to combinations of retinol boosters selected from, for example, the CTFA library of compounds. These combinations are formed only between components which all display significant activity in some particular in-vitro assay (page 7, lines 21-25). Thus, Granger et al, like Stockwell et al, teaches a method for identifying synergistic combinations by first testing the components from a library individually and then forming combinations only between components which display significant activity.

In contrast, in applicant's method, combinations are formed between components that display significant activity and substantially all the remaining components of the library.

Thus, Granger et al also teaches away from applicant's method.

In view of the above arguments applicant respectfully requests that the 103(a) rejection of claims 4-6 over Stockwell et al (US 2002/0019011) in view of Granger (WO 02/02074) be reconsidered and withdrawn.

Claims 15-17 were rejected under 35 USC 103(a) as being unpatentable over Stockwell et al (US 2002/0019011) as applied to claims 1-2 and 27 above in view of Guy, J Invest Dermatology, 110:410-415 (1998) and further in view of Zouboulis, JEADV, 15, Suppl. 3:63-67 (2001). Applicant traverses this rejection.

Stockwell et al has already been discussed.

Since neither Guy nor Zouboulis remedy the shortcomings of Stockwell et al as applied to claims 1, 2 and 27 (as well as claims 24-26), the combination of references do not present a *prima facie* case of obviousness.

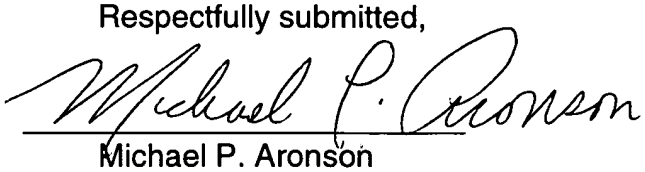
In view of the above arguments, applicant respectfully requests that the 103(a) rejection over Stockwell et al (US 2002/0019011) in view of Guy, J Invest Dermatology, 110:410-415 (1998) and further in view of Zouboulis, JEADV, 15, Suppl. 3:63-67 (2001) be reconsidered and withdrawn.

In summary, applicant's method is not intuitively obvious, with its emphasis on repeatedly testing entities that have repeatedly failed while not taking forward to future cycles many effective combinations. However, surprisingly, this approach does result in the identification of the most effective combination out of the whole library – although it fails to identify vast numbers of lesser effective combinations. This general methodology coupled with the high throughput multi-pathway assays and scaling procedures disclosed, makes the quest for synergy in large libraries of compounds practical and is an advance in the art.

In view of the foregoing amendment and comments, applicant respectfully requests the Examiner to reconsider the rejection and now allow the claims.

If a telephone conversation would be of assistance in advancing prosecution of the subject application, applicants' undersigned agent invites the Examiner to telephone him at the number provided.

Respectfully submitted,



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